

**Amendments to the claims:**

This listing of claims replaces all prior versions, and listings, of claims in the application.

**Listing of claims:**

- 1 (withdrawn): A method of diagnosing or prognosticating a neurodegenerative disease in a subject, or determining whether a subject is at increased risk of developing said disease, comprising:  
  
determining a level and/or an activity of
  - (i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
  - (ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
  - (iii) a fragment, or derivative, or variant of said transcription or translation productin a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby diagnosing or prognosticating said neurodegenerative disease in said subject, or determining whether said subject is at increased risk of developing said neurodegenerative disease.

2 (withdrawn): A method of monitoring the progression of a neurodegenerative disease in a subject, comprising:

determining a level and/or an activity of

(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product in a sample obtained from said subject and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby monitoring the progression of said neurodegenerative disease in said subject.

3 (withdrawn): A method of evaluating a treatment for a neurodegenerative disease, comprising: determining a level and/or an activity of

(i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or

(iii) a fragment, or derivative, or variant of said transcription or translation product,

in a sample obtained from a subject being treated for said disease and comparing said level and/or said activity to a reference value representing a known disease or health status, thereby evaluating said treatment for said neurodegenerative disease.

- 4 (withdrawn): The method according to claim 1 wherein said neurodegenerative disease is Alzheimer's disease.
- 5 (withdrawn): The method according to claim 1 wherein said sample comprises a cell, or a tissue, or a body fluid, in particular cerebrospinal fluid or blood.
- 6 (withdrawn): The method according to claim 1 wherein said reference value is that of a level and/or an activity of
- (i) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
  - (ii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
  - (iii) a fragment, or derivative, or variant of said transcription or translation product,
- in a sample obtained from a subject not suffering from said neurodegenerative disease.

- 7 (withdrawn): The method according to claim 1 wherein an alteration in the level and/or activity of a transcription product of the gene coding for the minor vault protein ADPRTL1 and/or a translation product of a gene coding for the minor vault protein ADPRTL1, and/or a fragment, or derivative, or variant thereof, in a sample cell, or tissue, or body fluid, in particular cerebrospinal fluid, obtained from said subject relative to a reference value representing a known health status indicates a diagnosis, or prognosis, or increased risk of Alzheimer's disease in said subject.
- 8 (withdrawn): A kit for diagnosing or prognosticating a neurodegenerative disease, in particular Alzheimer's disease, in a subject, or determining the propensity or predisposition of a subject to develop such a disease by:
- (i) detecting in a sample obtained from said subject a level, or an activity, or both said level and said activity of a transcription product and/or of a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, compared to a reference value representing a known health status; and said kit comprising:
    - a) at least one reagent which is selected from the group consisting of (i) reagents that selectively detect a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and (ii) reagents that selectively detect a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1.

9 (withdrawn): A method of treating or preventing a neurodegenerative disease, in particular AD, in a subject comprising administering to said subject in a therapeutically or prophylactically effective amount an agent or agents which directly or indirectly affect an activity and/or a level of

- (i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (iv) a fragment, or derivative, or variant of (i) to (iii).

10 (withdrawn): A modulator of an activity and/or of a level of at least one substance which is selected from the group consisting of

- (i) a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (ii) a transcription product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (iii) a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, and/or
- (iv) a fragment, or derivative, or variant of (i) to (iii).

- 11 (withdrawn): A recombinant, non-human animal comprising a non-native gene sequence coding for a vault protein, the minor vault protein ADPRTL1, or a fragment, or a derivative, or a variant thereof, said animal being obtainable by:
- (i) providing a gene targeting construct comprising said gene sequence and a selectable marker sequence, and
  - (ii) introducing said targeting construct into a stem cell of a non-human animal, and
  - (iii) introducing said non-human animal stem cell into a non-human embryo, and
  - (iv) transplanting said embryo into a pseudopregnant non-human animal, and
  - (v) allowing said embryo to develop to term, and
  - (vi) identifying a genetically altered non-human animal whose genome comprises a modification of said gene sequence in both alleles, and
  - (vii) breeding the genetically altered non-human animal of step (vi) to obtain a genetically altered non-human animal whose genome comprises a modification of said endogenous gene, wherein said disruption results in said non-human animal exhibiting a predisposition to developing symptoms of a neurodegenerative disease or related diseases or disorders.
- 12 (withdrawn): The animal according to claim 11 wherein said minor vault protein ADPRTL1 is the minor vault protein of SEQ ID NO. 2.

- 13 (withdrawn): Use of the recombinant, non-human animal according to claim 11 for screening, testing, and validating compounds, agents, and modulators in the development of diagnostics and therapeutics to treat neurodegenerative diseases, in particular Alzheimer's disease.

Claims 14 and 15 (cancelled).

- 16 (withdrawn): The method according to claim 15 wherein said test animal and/or said control animal is a recombinant animal which expresses a vault protein, the minor vault protein ADPRTL1 or a fragment, or a derivative, or a variant thereof, under the control of a transcriptional control element which is not the native vault protein gene transcriptional control element.
- 17 (withdrawn): An assay for testing a compound, preferably for screening a plurality of compounds for inhibition of binding between a ligand and a vault protein, the minor vault protein ADPRTL1 or a fragment, or derivative, or a variant thereof, said assay comprising the steps of:
- (i) adding a liquid suspension of said vault protein, or a fragment, or a derivative, or a variant thereof, to a plurality of containers;
  - (ii) adding a compound, preferably a plurality of compounds, to be screened for said inhibition of binding to said plurality of containers;

- (iii) adding a detectable ligand, in particular a fluorescently detectable ligand, to said containers;
  - (iv) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds, and said ligand;
  - (v) measuring amounts of detectable ligand or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and
  - (vi) determining the degree of inhibition by one or more of said compounds of binding of said ligand to said vault protein, or said fragment, or derivative, or variant thereof.
- 18 (withdrawn): An assay for testing a compound, preferably for screening a plurality of compounds to determine the degree of binding of said compounds to a vault protein, the minor vault protein ADPRTL1, or to a fragment, or derivative, or variant thereof, said assay comprising the steps of:
- (i) adding a liquid suspension of said vault protein, or a fragment, or derivative, or variant thereof, to a plurality of containers;
  - (ii) adding a detectable compound, preferably a plurality of detectable compounds, in particular fluorescently detectable compounds, to be screened for said binding to said plurality of containers;
  - (iii) incubating the liquid suspension of said vault protein, or said fragment, or derivative, or variant thereof, and said compound, preferably said plurality of compounds;



- (iv) measuring amounts of detectable compound or fluorescence associated with said vault protein, or with said fragment, or derivative, or variant thereof; and
  - (v) determining the degree of binding by one or more of said compounds to said vault protein, or said fragment, or derivative, or variant thereof.
- 19 (withdrawn): Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a diagnostic target for detecting a neurodegenerative disease, preferably Alzheimer's disease.
- 20 (withdrawn): Use of a protein molecule, said protein molecule being a translation product of the gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, as a screening target for reagents or compounds preventing, or treating, or ameliorating a neurodegenerative disease, preferably Alzheimer's disease.
- 21 (withdrawn): Use of an antibody specifically immunoreactive with an immunogen, wherein said immunogen is a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1, SEQ ID NO. 2, or a fragment, or derivative, or variant thereof, for detecting the pathological state of a cell in a sample obtained from a subject, comprising

immunocytochemical staining of said cell with said antibody, wherein an altered degree of staining, or an altered staining pattern in said cell compared to a cell representing a known health status indicates a pathological state of said cell, and wherein said pathological state relates to a neurodegenerative disease, in particular Alzheimer's disease.

22 (canceled).

23 (withdrawn): An assay for screening for a modulator of Alzheimer's disease, or a related disease or disorder, the method comprising

- a) contacting a cell with a test compound,
- b) measuring the activity and/or level of a nucleic acid substance in the contacted cell, wherein the substance is
  - i) a transcription product of a gene coding for minor vault protein ADPRTL1 (SEQ ID NO: 2),
  - ii) a derivative thereof, or
  - iii) a transcription product of a gene coding for minor vault protein ADPRTL1 (SEQ ID NO: 2) and a derivative thereof,
- c) measuring the activity and/or level of the nucleic acid substance in a control cell not contacted with the test compound, and

d) comparing the measured activity and/or level in the test cell with the measured activity and/or level in the control cell,

wherein an alteration in the measured activity and/or level in the contacted cell, from the measured activity and/or level in the control cell, indicates that the test compound is a modulator of the substance and, thereby, a modulator of Alzheimer's disease, or a related disease or disorder.

24 (new): An assay for screening for a modulator of the minor vault protein ADPRTL1, whereby said modulator is modulating substances consisting of a translation product of a gene coding for a vault protein, the minor vault protein ADPRTL1 as shown in SEQ ID NO: 2, and the method comprising:

- (a) contacting a cell with a test compound;
- (b) measuring the activity and/or level of the substances recited;
- (c) measuring the activity and/or level of the substances in a control cell not contacted with the test compound; and
- (d) comparing the levels and/or activities of the substances in the cells of step (b) and (c), wherein an alteration in the activity and/or level of substances in the contacted cells indicates that the test compound is a modulator of Alzheimer's disease.